106. The protein of claim 105, wherein the mutation in SEQ ID NO:137 is an A→T substitution at nucleic acid position 787.

107. The protein of claim 105, wherein the mutation in SEQ ID NO:137 is an A→G substitution at nucleic acid position 1080.

108. The protein of claim 103, wherein the splice variant encoded by the nucleic acid sequence comprising SEQ ID NO:137, which polynucleotide lacks a triplet GAA codon at nucleotide positions 1338-1340.

REMARKS

Reconsideration and allowance are respectfully requested. Claims 24, 71, 73-77, and 80-94 were pending. Claims 24, 71, 73-77, and 80-94 have been canceled and new claims 95-108 have been added in order to more particularly point out and distinctly claim the invention. The newly added claims find support in the original claims and throughout the specification (*see e.g.*, page 28, line 2-14; page 29, lines 13-18 and 25-27; page 30, lines 10-23). No new subject matter has been added. Thus, claims 95-108 are pending and at issue.

1. **The Claims are Definite and Clear**

Claims 24, 71-72, 74, 77, 80-82, 84, 85-86, and 88-94 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner asserted that the claims were indefinite for (1) not clearly defining the portions of SEQ ID NO:137 that were encompassed by the claim, (2) not clearly identifying the claimed mutations as occurring in the nucleic acid or protein sequence, and (3) not clearlyidentifying the number of mutations encompassed by the claims. The Examiner also alleged that the claims were unclear. The claims were canceled and the new claims utilize language that clearly identifies (1) the portions of SEQ ID NO:137 that are encompassed in the claim, (2) the claimed mutations as occurring in the nucleic acid or protein sequence, and (3) the number of mutations encompassed by the claims. Accordingly, the Applicants respectfully request that the objection be withdrawn.

The Examiner asserted that claims 24, 71, 74, 77, 79, 80-82, 84, 85-86, and 88-94 were indefinite for identifying the claimed protein with an unclear laboratory designation. The claims were canceled and the new claims utilize terminology that is now well known in the art to refer to the E5-1 protein. Support is found in the current terminology of the art, that references this protein as PS2. Furthermore, this "unclear laboratory designation" is fully defined by the specification. It is well settled that Applicants may be their own lexicographer. In this instance, they have explicitly defined a new term PS2 (E5-1) (See page 12, lines 19-23). Thus, this basis for rejection is in error and should be withdrawn.

Claims 73, 75, 76, and 87 were objected to as being dependent upon rejected base

claims. Based on the cancellation of these claims and the base claims, the objection is moot. Accordingly, the Applicant respectfully request that the objection be withdrawn.

2. **The Application Meets the Requirements of § 112, First ¶**

Enablement

Claims 24, 71, 74, and 77-79 were rejected under 35 U.S.C. § 112, first paragraph as not enabled. The Examiner asserts that the specifications, while enabling for E5-1 proteins that comprise or consist of the sequence of SEQ ID NO:138 (wild-type protein) and SEQ ID NO: 138 where the amino acids at position 141 and/or 239 have been replaced, do not provide enablement for other mammalian and human E5-1 proteins, mutations, and splice variants. The rejection is respectfully traversed and reconsideration is requested.

Applicants simply cannot understand, given the advanced state of the art of protein structure and sequence analysis, the basis for the rejection. Stated simply, one of ordinary skill, armed by the Applicants with the nucleic acid and amino acid sequences of PS2 (E5-1) would, by mere application of the readily available computer algorithms, have not the slightest difficulty in ascertaining whether a gene or its encoded protein represents a human PS2, *i.e.*, an allele of the specifically disclosed protein having an amino acid sequence of SEQ ID NO:138.

The Examiner cites several prior studies with acidic fibroblast growth factor,

transforming growth factor alpha, the β-chain of human insulin, interleukin (IL)-2, and bovine NPY Y3 receptor wherein a single amino acid modification resulted in altered activity of the novel protein. These references purportedly teach the unpredictability of introducing a functional mutation in a given protein. This is not in issue. However, these references emphatically establish Applicants' position: despite mutation, the protein can be identified unambiguously.

In each reference given by the Examiner, the amino acid sequence of the mutated protein is >99% identical to the native protein. The Examiner recognizes, as do the references, that the mutated proteins are clearly identifiable as variants of the wild-type, despite any altered activity. In short, these references prove the opposite of the Examiner's conclusion: variants of the proteins, regardless of altered function, are still identifiable as variants of the proteins. Thus, the claimed PS2 protein sequences are enabled due to the high degree of sequence homology between the mutated, allelic variants, splice variants, and wild-type proteins with SEQ ID NO:138.

Applicants describe and exemplify two splice variants and two muteins of the claimed nucleotide and protein sequences (page 28, lines 2-14; page 29, lines 13-15 and lines 25-27; page 30, lines 10-18). Furthermore, the specification describes nucleotide and sequence homology to human and non-mammalian proteins (see page 27, lines 15-16; page 28, lines 27-31; page 28, lines 21-23; page 28, lines 23-25). The specification teaches that the presence of homologous species and regions of conserved amino acid sequence between proteins of the same

family; it is incomprehensible to suggest that allelic variants are not enabled. These disclosures clearly establish that the scope of invention that has been enabled extends well beyond the provided examples.

Applicants respectfully submit that by providing the specific sequences disclosed herein, coupled with the level of skill in the art as described above, the human PS2 (E5-1) allelic variants and muteins alleged by the Examiner not to be enabled are the readily available starting point of enablement of the present invention given the advanced level of skill in the art and the routine nature of the these techniques (See Sambrook *et al.*, Molecular Cloning: A Laboratory Manual 2nd Edition, 1989). Applicants should not have to explain evaluating homology using one of the plethora of available programs (such as BLAST; See pages 20, lines 13-19 and page 27, lines 11-16), once a specific gene has been identified and described. These techniques of evaluating homology are routine. Accordingly, the Applicants respectfully request that the objection be withdrawn.

Written Description

Claims 24, 71, 74, 77, 80-86, and 88-89 were rejected under 35 U.S.C § 112, first paragraph, as allegedly containing matter that lacked sufficient written description to establish that Applicants had possession at the time of filing of the breadth of the claims. The Examiner alleges that the written description only sets forth the isolated E5-1 proteins (1) that comprise or consist of the sequence of SEQ ID NO:137 or 138, (2) SEQ ID NO: 138 where the amino acids

at position 141 and/or 239 have been replaced, and (3) that are encoded by SEQ ID NO: 138, wherein the A nucleotide is substituted by a T at position 787 and/or the A nucleotide is substituted by a G at position 1080. The rejection is respectfully traversed and reconsideration is requested.

As described in the previous section concerned with enablement of the scope of the claims, the Applicants have provided examples, where one should, of human PS2 (E5-1) sequences, *i.e* allelic variants. The specification discloses relevant identifying nucleotide and amino acid sequence information (page 12, line19 to page 13, line 1; page 28, lines 2-10; page 29, lines 13-15, page 30, lines 10-18) that is more than representative of a sufficient number of protein species to establish entitlement to the claimed genus. Applicants clearly had possession of all human variants. To suggest otherwise, defies scientific credibility as well as the express description of the specification.

The Examiner has clearly failed to consider the advanced state of the art at the time this invention was made. The description of a sequence and information on nucleotide and amino acid sequence homology to similar proteins serves to establish to one of skill in the art that Applicants are fully possessed of an invention at least as broad as the claims here.

In view of the foregoing remarks, Applicants submit that the Examiner's rejections under 35 U.S.C. § 112, first paragraph, are obviated or overcome and should be withdrawn.

CONCLUSION

Applicants request entry of the foregoing remarks in the file history of this application. If there are any remaining issues, please contact the undersigned attorney for a pplicant by telephone. Allowance of the application is earnestly solicited.

Respectfully submitted,

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